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Synthesis of C_1-symmetric chiral tripodal oxazolines through an oxazoline exchange reaction with amino alcohols

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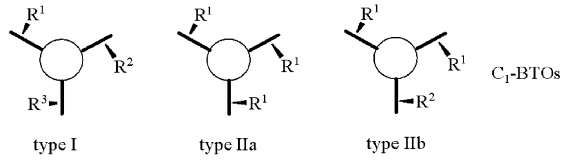
Abstract—Various C_1-symmetric chiral tripodal tris(oxazolines) with two different oxazoline units were synthesized from chiral C_3-symmetric tris(oxazolines) through an oxazoline exchange reaction with amino alcohols in the presence of zinc chloride. Evaluation of the new oxazolines as chiral molecular receptor showed that some of the receptors have chiral discrimination ability.

Oxazolines are useful metal ligands in asymmetric catalysts[1] and also important heterocycles found in various natural products.[2] Chiral oxazolines are usually prepared by coupling of carboxylic acids with amino alcohols followed by ring formation or by direct condensation of nitriles with amino alcohols in the presence of a Lewis acid such as zinc chloride.[3] Among chiral oxazolines, C_2-symmetric bis(oxazolines) have been widely used in metal-catalyzed asymmetric catalysis.[4] Recently we introduced C_3-symmetric tripodal oxazolines, which have several unique features as artificial receptors.[5] We also demonstrated that the C_3-symmetric tripodal oxazolines are potentially useful ligands for potassium enolates in an asymmetric conjugate addition reaction.[6] Our tripodal oxazolines provide a C_3-symmetric 'screw-sense' chiral environment upon binding organoammonium or potassium ions. During the studies, we became interested in tripodal oxazolines of C_1-symmetry, that is, non-C_3-symmetric, which would provide a different chiral environment.[7] In an effort to synthesize C_1-symmetric tripodal oxazolines, we have found that oxazoline rings undergo an exchange reaction with amino alcohols in the presence of zinc chloride. Herein, we wish to report a novel synthesis of C_1-symmetric tripodal oxazolines through the oxazoline exchange reaction.

To synthesize C_1-symmetric benzene-based tripodal oxazolines (C_1-BTOs), several approaches are possible. One is to introduce three oxazoline rings with at least one different substituent that provide the screw-sense chirality, depicted as type I ($R^1 = R^2 \neq R^3$ or $R^1 \neq R^2 \neq R^3$, oxazoline substituents at C-5).



Another approach to synthesize C_1-BTOs is to introduce one oxazoline ring, of which substituent has the opposite stereochemistry to that of the other two (type II C_1-BTOs). In this case, we can use either the same oxazolines (type IIa) or different ones (type IIb; $R^1 \neq R^2$). We studied the latter approach. The type II oxazolines seem to provide a chiral environment of marked steric difference compared to type I.

To synthesize the type II C_1-BTOs in which $R^1 \neq R^2$, we first studied the introduction of third oxazoline part into a bis(oxazoline) precursor, **1a**, as shown in Scheme 1.

The bis(oxazoline) **1a** was prepared from tris(cyanomethyl)mesitylene by treatment with L-valinol in the presence of zinc chloride (1.2 equiv) in refluxing chlorobenzene for 60 h in 15% isolated yield, together with 34% of the corresponding tris(oxazolines) (**2a**).[5] Treatment of

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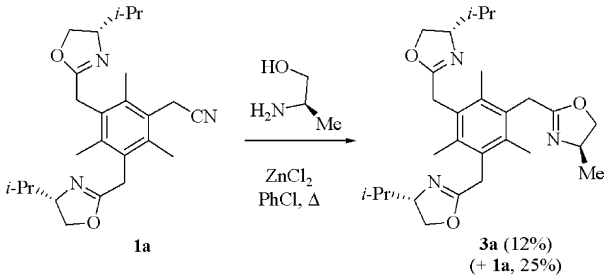
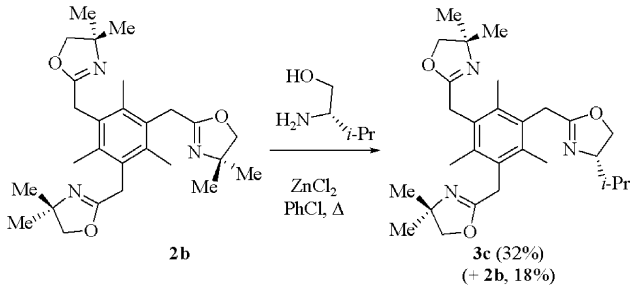
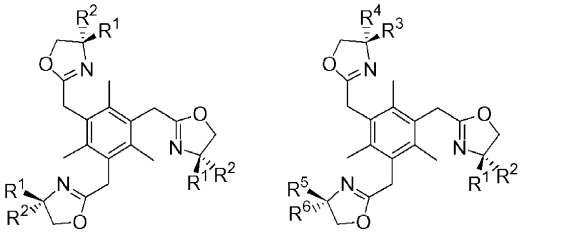


Scheme 1. Synthesis of *C*-BTO **3a** from bis(oxazoline) **1a**.



Scheme 2. Synthesis of C_1-BTO **3c** from C_3-BTO **2b** through oxazoline exchange mediated by $ZnCl_2$.

bis(oxazoline) **1a** with D-alaninol under similar reaction conditions afforded C_1-BTO **3a** in 12% isolated yield, together with recovered **1a** in 25% yield.



2a R^1 = H, R^2 = *i*Pr
2b R^1 = R^2 = Me
2c R^1 = Me, R^2 = H
2d R^1 = H, R^2 = Ph
2e R^1 = H, R^2 = H

3a R^1 = Me, R^2 = R^3 = R^5 = H, R^4 = R^6 = *i*Pr
3b R^1 = R^2 = Me, R^3 = R^5 = H, R^4 = R^6 = *i*Pr
3c R^1 = R^2 = R^3 = R^4 = Me, R^5 = H, R^6 = *i*Pr
3d R^1 = R^3 = Me, R^2 = R^4 = R^5 = H, R^6 = *i*Pr
3e R^1 = R^3 = Me, R^2 = R^4 = R^5 = H, R^6 = Ph
3f R^1 = Me, R^2 = R^3 = R^5 = H, R^4 = R^6 = Ph
3g R^1 = R^2 = R^3 = R^5 = H, R^4 = R^6 = Ph

Changing the amino alcohol, from D-alaninol to 2-amino-2-methyl-1-propanol, provided the corresponding C_1-BTO (**3b**) in 26% yield, recovered starting material (5%), and an unexpected product in 12% yield. The unexpected product was found to be C_1-BTO **3c**. This result indicated that an oxazoline could be converted into another oxazoline through an exchange reaction with an added amino alcohol under the reaction conditions. Based on this finding we investigated the exchange reaction for the tripodal oxazolines **2** to synthesize various C_1-BTOs **3**. The exchange reaction occurred generally for the oxazolines examined. For example, treatment of tris(oxazoline) **2b** with L-valinol (1.5 equiv) in the presence of zinc chloride (1.2 equiv) in refluxing chlorobenzene for 12 h afforded C_1-BTO **3c** in 32% yield, with recovered starting **2b** in 18% yield (Scheme 2).

Compared to the synthetic route that starts with bis(oxazoline) **1a** (Scheme 1), this exchange route was much more efficient and provided various C_1-BTOs in higher yields. The results are summarized in Table 1.[8] Using 1.5 equiv of amino alcohols, usually 'mono-exchanged' products were produced in 30–34% yields with recovered starting oxazolines (18–43% yields) (entries 3–5). When 2.4 equiv of amino alcohols were used, 'di-exchanged' products were produced in 17–20% yields along with mono-exchanged products (10–12% yields) (entries 6 and 7). Thus, the oxazoline exchange reaction is useful for the synthesis of tris(oxazolines) composed of different oxazolines, which are otherwise difficult to synthesize by known methods. Although a metal-catalyzed *trans*-amidation reaction is known,[9] to the best of our knowledge, this is the first example of metal-catalyzed oxazoline exchange reaction with amino alcohols.[10]

Considering the importance of bis- and tris(oxazoline) ligands in catalytic asymmetric reactions and molecular recognitions, this oxazoline exchange reaction may also be potentially useful in constructing libraries of oxazoline ligands from a variety of chiral amino alcohols available.

We briefly evaluated C_1-BTOs **3a–g** as chiral molecular receptors toward an α-phenylethylammonium ion by the extraction method as we reported.[5c] All the receptors showed high percent extraction, indicating that they

Table 1. Synthesis of C_1-BTOs **3** from bis- and tris(oxazolines) **1a** and **2** mediated by $ZnCl_2$[a]

Entry	Reactant	Amino alcohol (equiv)[b]	Temp (°C)[c]	Time (h)	Product (yield %)[d]
1	**1a**	D-Alaninol (2.4)	Reflux	120	**3a** (12), **1a** (25)
2	**1a**	2-Amino-2-methyl-1-propanol (3.0)	Reflux	72	**3b** (26), **3c** (12), **1a** (5)
3	**2b**	L-Valinol (1.5)	Reflux	12	**3c** (32), **2b** (18)
4	**2c**	L-Valinol (1.5)	80	12	**3d** (30), **3a** (6), **2c** (43)
5	**2c**	L-Phenylglycinol (1.5)	100	6	**3e** (34), **2c** (18)
6	**2c**	L-Phenylglycinol (2.4)	100	24	**3f** (20), **3e** (12)
7	**2e**	L-Phenylglycinol (2.4)	100	24	**3g** (17), **2d** (10)

[a] 1.2 molar equiv of $ZnCl_2$ are used.
[b] The numbers in parentheses are molar equiv used.
[c] Chlorobenzene as the solvent.
[d] Isolated yields after column chromatography on SiO_2; other minor side products are not included.

are stronger binders toward ammonium ion. A significant chiral discrimination was observed in the cases of C_1-BTOs **3e**–**g**, whereas little enantioselection was observed in the cases of other receptors. For example, with C_1-BTO **3f** 100% extraction and an enantioselection of 59(*S*):41(*R*) were obtained, and with **3g** 80% extraction and an enantioselection of 58(*S*):42(*R*) were obtained. Thus, only those C_1-BTOs that have phenyl-substituted oxazolines show substantial enantioselection, which implies that the oxazoline substituent plays an important role in the chiral discrimination. Also, the enantioselectivity observed with the C_1-BTOs are lower than that observed with the C_3-symmetric PhBTO.[5c] These results raise questions on the enantioselection mechanism with the C_1-BTOs in comparison with the C_3-PhBTO.

In conclusion, we have synthesized various chiral tripodal oxazolines that have C_1-symmetry. The synthesis involved a novel zinc chloride-promoted oxazoline exchange reaction with added amino alcohols. A preliminary study showed that some of the C_1-BTOs also have chiral discrimination ability toward an α-phenylethylammonium ion. A further study on the chiral discrimination mechanism and catalytic asymmetric reactions with the C_1-BTOs are under investigation and will be reported elsewhere.

Acknowledgements

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467.3142. Compound **3b**: $R_f = 0.33$ (1:9 MeOH/EtOAc); mp 158–159 °C; $[\alpha]_D^{25} - 77.2$ (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.17–4.09 (m, 2H), 3.91–3.82 (m, 6H), 3.70 (s, 4H), 3.67 (s, 2H), 2.35 (s, 9H), 1.76–1.68 (m, 2H), 1.22 (s, 6H), 0.82 (d, $J = 6.8$ Hz, 6H), 0.90 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 164.4, 136.3, 136.2, 131.2, 131.1, 79.5, 72.1, 70.1, 67.2, 32.7, 30.7, 30.5, 28.7, 19.2, 18.2, 17.5, 17.4, 17.3; MS (EI) *m/z* (rel intensity) 481 (M^+, 100), 467 (32), 396 (22); HRMS (EI) calcd for $C_{29}H_{43}N_3O_3$: 481.3302, found: 481.3310. Compound **3c**: $R_f = 0.26$ (0.5:9.5 MeOH/EtOAc); mp 166–167 °C; $[\alpha]_D^{25} - 33.4$ (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.16–4.10 (m, 1H), 3.91–3.82 (m, 6H), 3.70 (s, 2H), 3.68 (s, 4H), 2.36 (s, 9H), 1.79–1.68 (m, 1H), 1.22 (s, 12H), 0.82 (d, $J = 6.8$ Hz, 6H), 0.90 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 164.4, 136.2, 131.1, 131.0, 79.5, 72.1, 70.1, 67.2, 32.7, 30.7, 30.5, 28.7, 19.2, 18.1, 17.5, 17.4; MS (EI) *m/z* (rel intensity) 467 (M^+, 100), 453 (24), 396 (33); HRMS (EI) calcd for $C_{28}H_{41}N_3O_3$: 467.3148, found: 467.3143. Compound **3d**: $R_f = 0.24$ (1:9 MeOH/EtOAc); mp 126–127 °C; $[\alpha]_D^{25} + 15.7$ (*c* 1.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 4.27 (dd, $J = 9.3$, 8.1 Hz, 2H), 4.16–4.07 (m, 3H), 3.93–3.86 (m, 2H), 3.76–3.64 (m, 8H), 2.36 (s, 9H), 1.80–1.69 (m, 1H), 1.20 (d, $J = 6.5$ Hz, 6H), 0.84 (d, $J = 6.8$ Hz, 6H), 0.91 (d, $J = 6.8$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 165.8, 136.1, 136.0, 131.1, 131.0, 74.4, 72.1, 70.1, 61.7, 30.7, 30.4, 21.9, 19.2, 18.2, 17.5, 17.4; HRMS (EI) calcd for $C_{26}H_{37}N_3O_3$: 439.2835, found: 439.2848. Compound **3e**: $R_f = 0.48$ (5:95 MeOH/EtOAc); mp 89–90 °C; $[\alpha]_D^{25} + 24.4$ (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.20 (m, 5H), 5.14 (t, $J = 8.7$ Hz, 1H), 4.58 (dd, $J = 10.2$, 8.4 Hz, 1H), 4.28 (dd, $J = 9.3$, 8.1 Hz, 2H), 4.13–4.05 (m, 2H), 4.04 (dd, $J = 8.4$, 8.1 Hz, 1H), 3.83 (s, 2H), 3.72 (t, $J = 7.8$ Hz, 2H), 3.67 (s, 4H), 2.42 (s, 6H), 2.37 (s, 3H), 1.20 (d, $J = 6.6$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 165.8, 143.0, 136.3, 136.2, 131.2, 131.1, 129.0, 127.8, 127.0, 75.3, 74.4, 69.8, 61.7, 30.5, 21.9, 17.5, 17.4; MS (EI): *m/z* (rel intensity) 473 (M^+, 100), 442 (20), 416 (15); HRMS (EI) calcd for $C_{29}H_{35}N_3O_3$: 473.2678, found: 473.2672. Compound **3f**: $R_f = 0.62$ (0.5:9.5 MeOH/EtOAc); mp 75–76 °C; $[\alpha]_D^{25} - 20.4$ (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32–7.19 (m, 10H), 5.14 (dd, $J = 10.1$, 8.3 Hz, 2H), 4.57 (dd, $J = 10.1$, 8.5 Hz, 2H), 4.28 (dd, $J = 9.3$, 8.1 Hz, 1H), 4.15–4.10 (m, 1H), 4.04 (dd, $J = 8.5$, 8.3 Hz, 2H), 3.84 (s, 4H), 3.77 (t, $J = 7.6$ Hz, 1H), 3.72 (s, 2H), 2.48 (s, 3H), 2.43 (s, 6H), 1.20 (d, $J = 6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 165.8, 143.0, 136.3, 136.2, 131.3, 131.0, 129.0, 127.8, 127.0, 75.3, 74.4, 69.9, 61.7, 30.5, 21.9, 17.7, 17.6; MS (EI): *m/z* (rel intensity) 535 (M^+, 100), 505 (22), 414 (15); HRMS (EI) calcd for $C_{34}H_{37}N_3O_3$: 535.2835, found: 535.2826. Compound **3g**: $R_f = 0.45$ (1:9 MeOH/EtOAc); mp 44–45 °C; $[\alpha]_D^{25} - 44.8$ (*c* 0.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.19 (m, 10H), 5.14 (dd, $J = 10.2$, 8.3 Hz, 2H), 4.57 (dd, $J = 10.2$, 8.4 Hz, 2H), 4.21 (t, $J = 9.4$ Hz, 2H), 4.04 (dd, $J = 8.4$, 8.3 Hz, 2H), 3.85 (s, 4H), 3.75 (t, $J = 9.4$ Hz, 2H), 3.71 (s, 2H), 2.48 (s, 3H), 2.42 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.6, 167.1, 143.0, 136.2, 131.3, 131.0, 129.0, 127.8, 127.0, 126.3, 75.3, 69.9, 67.9, 54.7, 30.5, 30.3, 17.7, 17.6; MS (EI): *m/z* (rel intensity) 521 (M^+, 100), 491 (20); HRMS (EI) calcd for $C_{33}H_{35}N_3O_3$: 521.2678, found: 521.2676.

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